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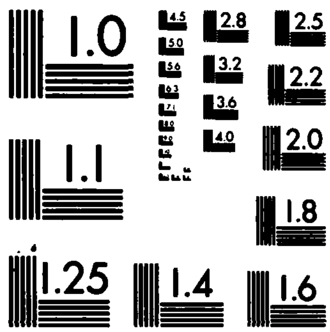

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RESUSCITATION OF HYPOTHERMIC-HYPOVOLEMIC-HYPOTENSIVE BABOONS

by

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ABSTRACT

Because baboon hemodynamics, lung function, oxygen transport function, clotting proteins, and platelet function are similar to those of man, we made a study of hypothermic, hypovolemic, hypotensive baboons to evaluate treatment programs.

When the temperature of the animal was reduced from 37 C to 32 C, a prolonged bleeding time was observed without thrombocytopenia. When the cold extremity was warmed, the prolonged bleeding time was corrected. These observations support the recommendation that warming a lacerated hypothermic extremity will reduce blood loss.

When the hypothermic, hypovolemic, hypotensive baboon was treated with previously frozen washed red cells and citrated fresh frozen plasma, we observed electromechanical dissociation of the heart and subsequent treatment with calcium chloride corrected this disorder. There was no increase in total oxygen consumption, limb oxygen consumption, or cardiac output associated with the exchange transfusion and resuscitation with red blood cells with 125 percent of normal 2,3 DPG levels compared to red cells with 40 percent of normal 2,3 DPG levels. The infusion of red cells with 125 percent of normal 2,3 DPG did produce significantly elevated 2,3 DPG levels, elevated in vitro and in vivo P_{50} values, and elevated mixed venous pO_2 tensions, compared to the infusion of red cells with 40 percent of normal 2,3 DPG.

In subsequent studies, we plan to compare this program of treatment using resuscitation followed by rewarming with treatment by rewarming

followed by resuscitation and a program of simultaneous resuscitation and rewarming. The data show that citrated fresh frozen plasma precipitated cardiac irritability in hypothermic, hypovolemic, hypotensive baboons. The baboon serves as an excellent model for studying the etiology, prevention and treatment of the bleeding diathesis and cardiac arrhythmia associated with hypothermia, hypovolemia and hypotension, and data obtained from baboon studies can be used in planning a program of treatment for humans suffering from these conditions.

INTRODUCTION

During hypothermia, the peripheral circulation is adversely affected by both hypovolemia and hypotension, and frostbite and immersion foot may develop. The individual's state of hydration, which is influenced by the intake of both salt and water, also is believed to influence tolerance to hypothermia and response to hypovolemia and hypotension during hypothermia. Various methods of treating this condition have been suggested, including resuscitation followed by rewarming, rewarming followed by resuscitation, and rewarming and resuscitation carried out simultaneously.

Several animals have been used to simulate human environmental conditions, injuries, and treatment programs.[1-10] A recent review summarizes what is known about resuscitation of hypothermic patients under clinical conditions.[11] The Naval Blood Research Laboratory at Boston University School of Medicine has been using baboons in these types of studies for more than 10 years because of the similarities in hemodynamics, pulmonary function, red cells, platelets, and clotting proteins, between humans and baboons.[12-28]

Individuals who have sustained traumatic injuries and hypothermic exposure are susceptible to cardiac arrhythmias, frostbite, and immersion foot. The life-threatening arrhythmias may be due to the effects of hypothermia on ionized calcium, potassium, and acid-base balance, and this condition may be aggravated when the hypothermia is treated by resuscitation with citrate-containing blood products.[29-37] It is not known whether hypothermic individuals are more susceptible to bleeding disorders, nor are the effects of hypothermia on hemostasis completely understood.[38]

In the studies reported here, we utilized hypothermic, hypovolemic, hypotensive baboons to determine how treatment by a program of resuscitation followed by rewarming affected the oxygen transport function, cardiopulmonary function, and the hemostatic system. In subsequent studies, treatment programs using rewarming followed by resuscitation and simultaneous rewarming and resuscitation will be compared with the above-described mode of treatment.

METHODS AND MATERIALS

Nine healthy adult baboons (Papio papio and Papio cynocephalus) were studied, and four of these baboons were studied on two occasions. In the first phase of the study baboons received red cells with 40 percent of normal 2,3 DPG or red cells with 125 percent of normal 2,3 DPG. The second phase of the study was conducted two to three months after the first, and the mode of treatment was reversed, i.e., the baboons that received low 2,3 DPG red cells in the first phase received 125 percent of normal 2,3 DPG red cells in the second phase, and the others received 40 percent of normal 2,3 DPG red cells.

Some of the units of red cells were stored at 4 C for four to eight days and then frozen with 40 percent W/V glycerol and stored at -80 C (nonrejuvenated red cells) with 40 percent of normal 2,3 DPG levels.[24] Other units were stored at 4 C for four to eight days, biochemically treated with a 50 ml volume of a solution containing 50 mM/l pyruvate, 50 mM/l inosine, 100 mM/l glucose, 50 mM/l disodium phosphate and 5 mM/l adenine (PIGPA), and then frozen with 40 percent W/V glycerol and stored at -80 C (indated-rejuvenated red cells) with 125 percent of normal 2,3 DPG levels.[24] All units were thawed and washed on the day of infusion.

On the day of study each baboon was sedated with an intramuscular injection of Ketaset, intubated and ventilated with room air. Bilateral femoral cutdowns were made, and two nonocclusive arterial catheters, a thermal dilution pulmonary artery catheter, an electromagnetic femoral arterial flow probe, and a nonocclusive femoral vein catheter were placed using sterile technique and pressure monitoring. Cotton was placed in

the ears, and the eyes were taped shut to minimize animal anxiety. Pavulon, a paralyzing agent, was administered, and the Ketaset was allowed to wear off. This procedure has been reviewed and approved by the Veterinary Department at Boston University School of Medicine.

Baseline measurements were made of limb and total body oxygen consumption, arterial, pulmonary artery, and femoral vein pO_2, pCO_2, pH measured at 37 C and corrected to actual body temperature, bleeding time, in vivo and in vitro P_{50}, pulmonary shunt and deadspace. In vitro pH was measured using washed red cells in the Hemoscan at 37 C and at pH 7.2. Myocardial function was assessed by infusion of sodium chloride in standard aliquots and measuring pulmonary artery wedge pressure and cardiac output. Blood samples were collected for clotting studies and for measurement of lactate, red cell 2,3 DPG and ATP, glucose, phosphate, ionized and total calcium, albumin, total protein, platelet count, and oncotic pressure. The baseline measurements were repeated after cooling of the animal to 32 C with a hypothermic blanket.

The baboon then was made hypotensive by the withdrawal of blood to maintain mean blood pressure at 45 mm Hg for one-half hour; CPD was the anticoagulant used. All the previously listed measurements were repeated, both at initial shock and at 30 minutes of shock. After 30 minutes of hypothermic-hypovolemic-hypotensive shock while remaining in shock, each baboon was exchange-transfused with four units of previously frozen washed red cells; these red cells with a hematocrit value of 70 percent had either 40 percent or 125 percent of normal 2,3 DPG levels and were resuspended in saline. In addition, each animal received three units of fresh frozen CPD

baboon plasma. The exchange transfusion took about 50 minutes, during which time the animal's body temperature remained at 32 C and mean arterial pressure remained at 45 mm Hg. EKG, arterial pressure, and ionized calcium were closely monitored during this time. When electromechanical dissociation was observed, a blood sample for ionized calcium was obtained and 100 mg $CaCl_2$ was slowly infused intravenously. Ionized calcium was measured at 37 C and calcium chloride was infused to maintain the level of ionized calcium.

Immediately following the exchange transfusion, all the previously listed measurements were repeated, including bleeding time. Washed previously frozen baboon platelets were then infused, and the bleeding time was repeated. All measurements were repeated 30 minutes after exchange transfusion (total of about two hours in shock). Additional red cells and fresh frozen plasma were infused to raise the blood pressure to 80 mm Hg, and the measurements were repeated. The animal's body temperature was then warmed to 37 C; a crystalloid solution was infused to make the baboon normovolemic. All measurements were repeated. Ketaset was given, the Pavulon reversed, the lines removed, and the animal was awakened.

The same animals were used in the second phase of the study two to three months later. To minimize the chance of isosensitization, the red cells, platelets and plasma obtained during the initial phlebotomy and exchange transfusion were processed and frozen for use in the second phase of the study. The red cells had either 40 percent of normal 2,3 DPG or 125 percent of normal 2,3 DPG levels. In this second phase, treatment was reversed so that the 2,3 DPG level of the red cells administered was the

opposite of what the baboon had received in the first phase.

Bleeding time measurements. Template bleeding times were performed in duplicate in an upper extremity using an automated device (Simplate) while maintaining the capillary pressure at 40 mm Hg with the aid of a sphyngomanometer. Measurements were made before and after the baboon was cooled to 30-32 C, and after rewarming of the animal. Bleeding times also were measured after induction of shock, after exchange transfusion, and after platelet transfusion. In order to determine the cause of the prolonged bleeding time induced by hypothermia, whether due to abnormal platelet function or to altered vascular integrity, additional studies were performed. The baboons were cooled to 30-32 C and one arm was warmed to normal temperature with heating lights; bleeding times were measured on both the cold and warm arms.

Platelet function studies and blood coagulation proteins. Platelet aggregation to ADP, collagen, and arachidonic acid was measured prior to and after treatment of baboons with aspirin and prostacyclin (PGI_2). Beta thromboglobulin release was measured before and after cooling. Clotting tests and coagulation protein measurements were routinely performed at 37 C. In vitro coagulation tests also were done both at 30 C and at 37 C to determine the effect of temperature on these measurements. Baboons were tested before and after cooling and after rewarming for prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), fibrinogen, anti-thrombin III, and fibrin split products (FSP).

After the hypothermic baboons were bled into hemorrhagic shock, they were exchange-transfused first with previously frozen red cells and fresh

frozen plasma, and then with previously frozen platelets. The bleeding time was measured. The animal was rewarmed to 37 C, and the bleeding time was measured when 70-80 percent of the previously frozen platelets were in the circulation. The fresh frozen plasma and the cryopreserved platelets used in these studies had been collected before the study: the fresh frozen plasma was frozen and stored at -20 C, and the platelets were frozen with 6 percent DMSO and stored at -80 C as previously described.[27]

RESULTS AND DISCUSSION

Table 1 shows the similarities in prothrombin time, partial thromboplastin time, thrombin time, fibrinogen level, and Factor VIII activity between baboons and humans. All tests were performed with conventional reagents, and Factor VIII (AHF) assays were performed with human Factor VIII deficient substrate. Table 2 shows the similarities in platelet count, number of dense bodies per platelet, and platelet LDH activity, between humans and baboons. TABLE 1 TABLE 2

Baboons were treated with intravenous prostacyclin (PGI_2) and oral aspirin. An increase in bleeding time and an inhibition of platelet aggregation were observed following intravenous infusion of PGI_2, findings similar to those observed in man treated with PGI_2.

An increase in bleeding time and inhibition of platelet aggregation were observed following the oral ingestion of aspirin, findings similar to those observed in man.

The bleeding time of 3 minutes increased to 11 minutes during hypothermia in the cold arm, whereas the bleeding time of 2.5 minutes in the externally warmed arm increased to less than 4 minutes (Figure 1). Rewarming from 32 C to 37 C reduced the bleeding time to less than 4 minutes in both the cold arm and the warm arm. FIG. 1

Figure 2 is a schematic of the hypothermic-hypovolemic-hypotensive baboon. Each baboon was subjected to hypothermia to 32 C by external cooling with thermal blankets, to hypovolemia by reduction of blood volume by about 40 percent by phlebotomy, and to hypotension to a blood pressure

of 45 mm Hg for 30 minutes. Within 1 hour, during which time the baboon was in hypothermic-hypovolemic-hypotensive shock, an exchange transfusion of four units of previously frozen washed red cells with hematocrit values of 70 V percent resuspended in saline was given along with three units of citrated fresh frozen plasma. The 2,3 DPG level of these red cells was either 40 percent of normal or 125 percent of normal.

The animal was maintained in hypothermic-hypovolemic-hypotensive shock for 30 minutes after exchange transfusion, after which resuscitation with crystalloid solution, previously frozen washed red cells, previously frozen washed platelets, and citrated fresh frozen plasma, was instituted. Following resuscitation, the animal was rewarmed to 37 C with thermal blankets and warming lights.

The reduction in body temperature from 37 C to 32 C produced a significant increase in bleeding time in the cold extremity ($t = 3.724$, $p < 0.01$) but not in the warm extremity ($t = 0.8$, $p > 0.2$) (Figure 1 and Table 3) with no decrease in platelet count and no abnormality in platelet function as assessed by an increase in beta thromboglobulin. The baseline level of beta thromboglobulin when the temperature was 37 C was 54 $\pm$ 14 ng/ml in five baboons and after cooling to 32 C was 54 $\pm$ 9 ng/ml. The increase in bleeding time with hypothermia in the cold arm represented an alteration in vascular integrity and warming of the cold extremity reduced the bleeding time to normal. This finding suggests that warming of a lacerated cold extremity may help reduce blood loss, since bleeding time extension has been correlated to blood loss in patients subjected to cardiopulmonary bypass.[22] In baboons, the hemodynamic response to fluid

infusion during hypothermia was similar to that observed in humans (Table 4). TABLE 4

During hypothermia from 37 C to 32 C, there was no significant reduction in ionized calcium ($t = 0.075$, $p > 0.05$), a slight and significant increase in the in vivo arterial blood pH ($t = 4.4$, $p < 0.005$), and a slight and significant decrease in the in vivo pCO_2 ($t = 8.475$, $p < 0.001$), but no cardiac irritability (Tables 5-7). TABLES 5-7

Following phlebotomy and hypotension the baboon was exchange-transfused with previously frozen washed red cells with 40 percent or 125 percent of normal 2,3 DPG and citrated fresh frozen plasma. The fresh frozen plasma was needed to prevent the severe hypoproteinemia that occurred when only previously frozen washed red cells and crystalloid solution were exchange-transfused to the hypothermic-hypovolemic-hypotensive baboons. Electromechanical dissociation was observed in the nine baboons and the mean ionized calcium level was 1 mg/dl in seven of the nine baboons, and infusion of calcium chloride corrected this abnormality (Table 8). The TABLE 8 citrate present in the fresh frozen plasma reduced the ionized calcium and caused the electromechanical dissociation, and the calcium chloride restored the ionized calcium to normal and corrected the electromechanical dissociation.

Hypothermia inhibited the metabolism of citrate by the liver; the reduction in ionized calcium during hypothermia precipitated cardiac irritability. When blood products containing citrate are used to treat hypothermic patients, cardiac irritability may occur; calcium chloride infusions are indicated to treat the citrate-induced cardiac irritability

during the resuscitation of hypothermic patients in hypovolemic shock.

The hypothermic-hypovolemic-hypotensive baboons first exchange-transfused and then resuscitated with previously frozen washed red cells had similar total oxygen consumption, limb oxygen consumption, and cardiac output values whether the 2,3 DPG levels were 40 percent of normal or 125 percent of normal (Tables 9 and 10). The baboons receiving red cells with 125 percent of normal 2,3 DPG had significantly elevated ($p < 0.05$) red cell 2,3 DPG and in vivo and in vitro P_{50} values and increased mixed venous pO_2 tension ($p < 0.05$) compared to the baboons receiving red cells with 40 percent of normal 2,3 DPG. The cardiac response to volume loading was similar whether the red cells used during exchange transfusion and resuscitation of the hypothermic-hypovolemic-hypotensive baboon had 125 percent of normal or 40 percent of normal 2,3 DPG levels. Although red cells with 125 percent of normal 2,3 DPG levels improved oxygen availability to the tissue as manifested by increased in vivo P_{50} values and increased mixed pO_2 tensions, the use of these red cells during the resuscitation of hypothermic-hypovolemic-hypotensive baboons produced no increase in total oxygen consumption, limb oxygen consumption, or improvement in myocardial function.

TABLE 9
TABLE 10

Apstein and co-workers[39] reported that the perfusion of isolated rabbit hearts with human red cells with 150 percent of normal 2,3 DPG at normothermic and hypothermic temperatures produced greater improvement in oxygen consumption and myocardial function under basal conditions and after stimulation with isoproterenol than the perfusion with red cells with 20 percent of normal 2,3 DPG. The coronary blood flow was maintained

at a constant rate to simulate conditions of fixed coronary blood flow.

Hypothermia is known to increase the oxygen affinity of red cells, and in vitro studies made at the Naval Blood Research Laboratory have demonstrated that biochemically modified human red cells with increased 2,3 DPG (150 percent and 250 percent of normal) exhibit less affinity for oxygen at 24 C than red cells with 70 percent of normal 2,3 DPG.[40] Moreover, human red cells with 300 percent of normal 2,3 DPG levels perfused to isolated fibrillating dog hearts were found to produce significantly greater oxygen consumption, higher coronary sinus partial pressure of oxygen and carbon dioxide, higher in vitro P_{50} values, and lower arterial and coronary sinus lactate levels, than human red cells with 80 percent of normal 2,3 DPG, suggesting that high 2,3 DPG red cells might protect myocardial tissue in patients undergoing hypothermic cardiac operations.[41] In a study by Dennis and associates[42] in which patients coming off cardiopulmonary bypass were given either rejuvenated previously frozen washed red cells with 150 percent of normal 2,3 DPG or nonrejuvenated liquid-stored nonwashed red cells with 70 percent of normal 2,3 DPG, improved cardiac output was observed immediately following cardiopulmonary bypass when the high 2,3 DPG red cells were transfused. It has been suggested by some investigators that the improved cardiac output may have been due to the fact that the rejuvenated previously frozen red cells had been rendered free of citrate by the postthaw washing process, and that the citrate in the nonwashed nonrejuvenated red cells may have decreased the ionized calcium and impaired myocardial function.

In a more recent study by Jalonen and associates, red cells with

150 percent of normal 2,3 DPG levels and improved oxygen delivery led to a decrease in anaerobic metabolism and lactate production by the heart, without enhancement of cardiac output in the immediate reperfusion period during cardiopulmonary bypass.[43]

Admittedly, data collected thus far may not be sufficient to state that red cells with elevated 2,3 DPG levels are superior to red cells with normal 2,3 DPG levels.

Our studies on the hypothermic-hypovolemic-hypotensive baboon exchange-transfused and resuscitated with red cells with 125 percent of normal 2,3 DPG compared to 40 percent of normal 2,3 DPG red cells did not increase total and limb oxygen consumption or improve myocardial function even though mixed venous pO_2 tension was significantly increased. Red cells with slightly impaired oxygen transport and red cells with slightly improved oxygen transport function produced similar effects on total and limb oxygen consumption and cardiac output.

Studies will be performed in hypothermic-hypovolemic-hypotensive baboons to evaluate programs of treatment such as rewarming followed by resuscitation and rewarming and resuscitation simultaneously, for comparison of results with those obtained in this study.

Followin[illegible]othermia, hypovolemia and hypotension, the platelet count decrea[illegible] baseline of 248,000 to 172,000, the bleeding time in the cold a[illegible]reased from a baseline value of 4 minutes to 6 minutes, and in the warm arm the bleeding time was unchanged (Table 3). The hypothermic-hypovolemic-hypotensive baboon after exchange transfusion had a platelet count of 44,000; the bleeding time in the cold arm was

6 minutes and in the warm arm 5 minutes. After transfusion of previously frozen washed platelets the platelet count increased to 110,000, the bleeding time in the cold arm remained at 6 minutes and in the warm arm was increased to 9 minutes. After the baboon had been resuscitated to restore blood volume and blood pressure to normal and rewarmed to normothermia, the platelet count was 89,000 and the bleeding time was 6 minutes.

Bleeding time was influenced by hypothermia alone, and by hypothermia, hypovolemia and hypotension with and without thrombocytopenia. The increase in bleeding time with hypothermia alone was corrected by local warming of the extremity. The response of bleeding time to platelet transfusion was influenced by hypothermia, hypovolemia and hypotension.

The same protocols used in the preservation of human red cells, platelets and plasma proteins are used to preserve the baboon blood components. Using this animal as a study model, we will be able to evaluate the mechanism for the cardiac arrhythmia and bleeding diathesis associated with the hypothermic state alone and with the resuscitation of hypothermic, hypovolemic, hypotensive individuals, as well as the etiology, prevention and treatment of these disorders.

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FIGURE 1

The effect of hypothermia on the bleeding time and the platelet count in a baboon externally cooled to 32 C and rewarmed to 37 C. One arm was warmed externally by a heat lamp.

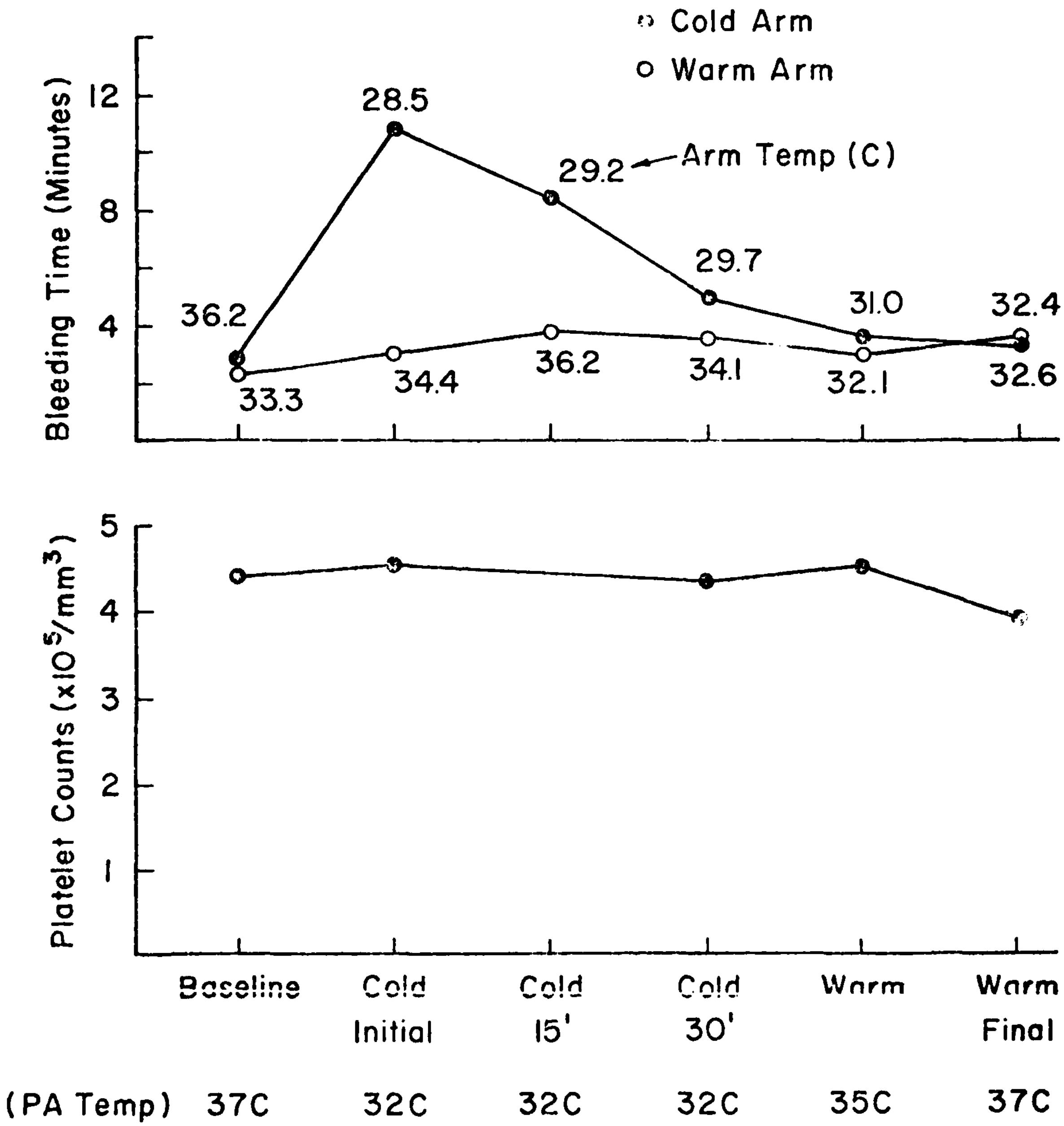

FIGURE 1

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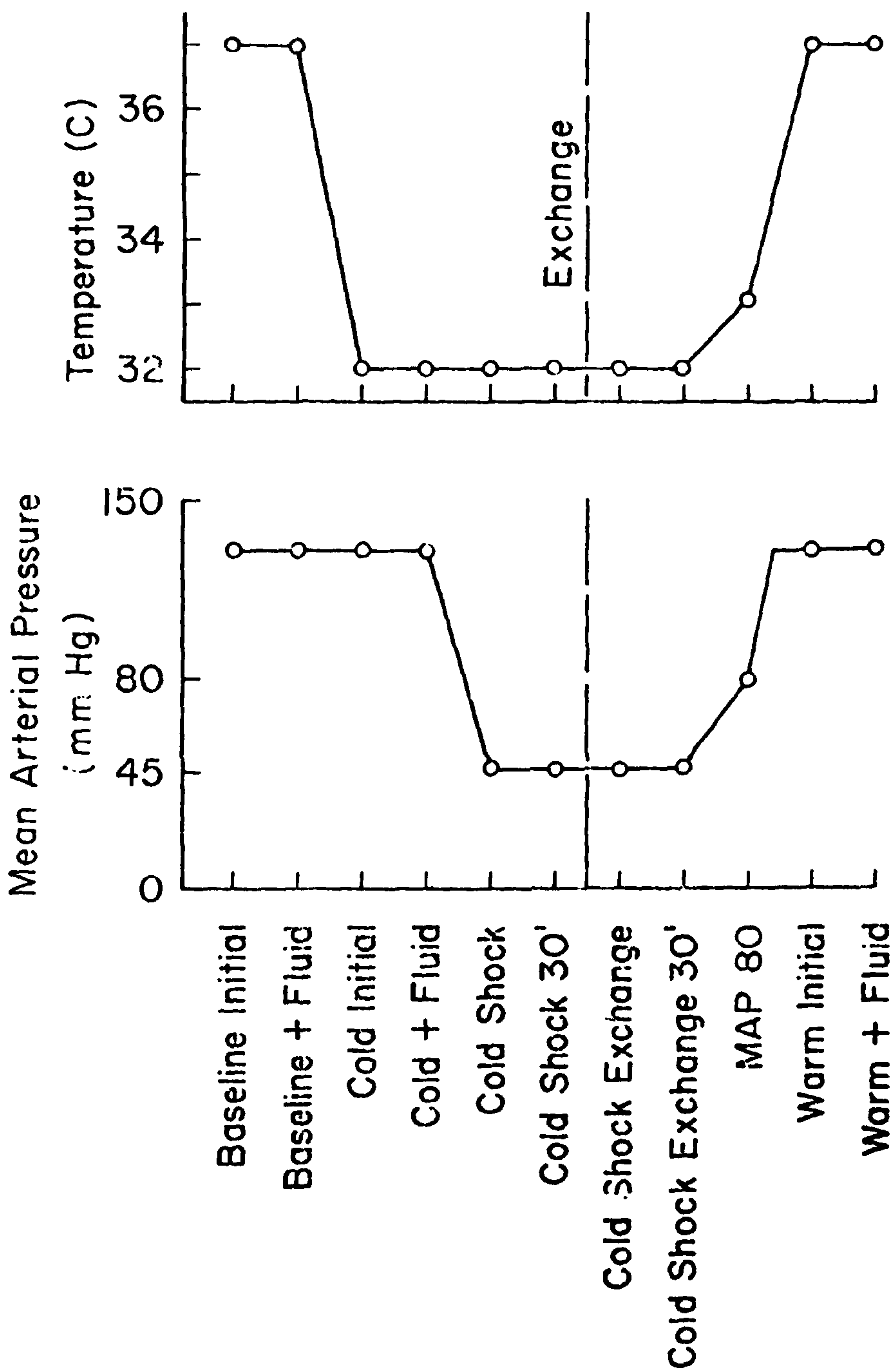
FIGURE 2

A schematic of the hypothermic, hypovolemic, hypotensive protocol in the baboon.



<u>FIGURE 2</u>

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FIGURE 3

The platelet count and bleeding time in hypothermic, hypovolemic, hypotensive baboons exchange transfused with previously frozen washed red blood cells and fresh frozen plasma and saline and then transfused with previously frozen washed platelets.

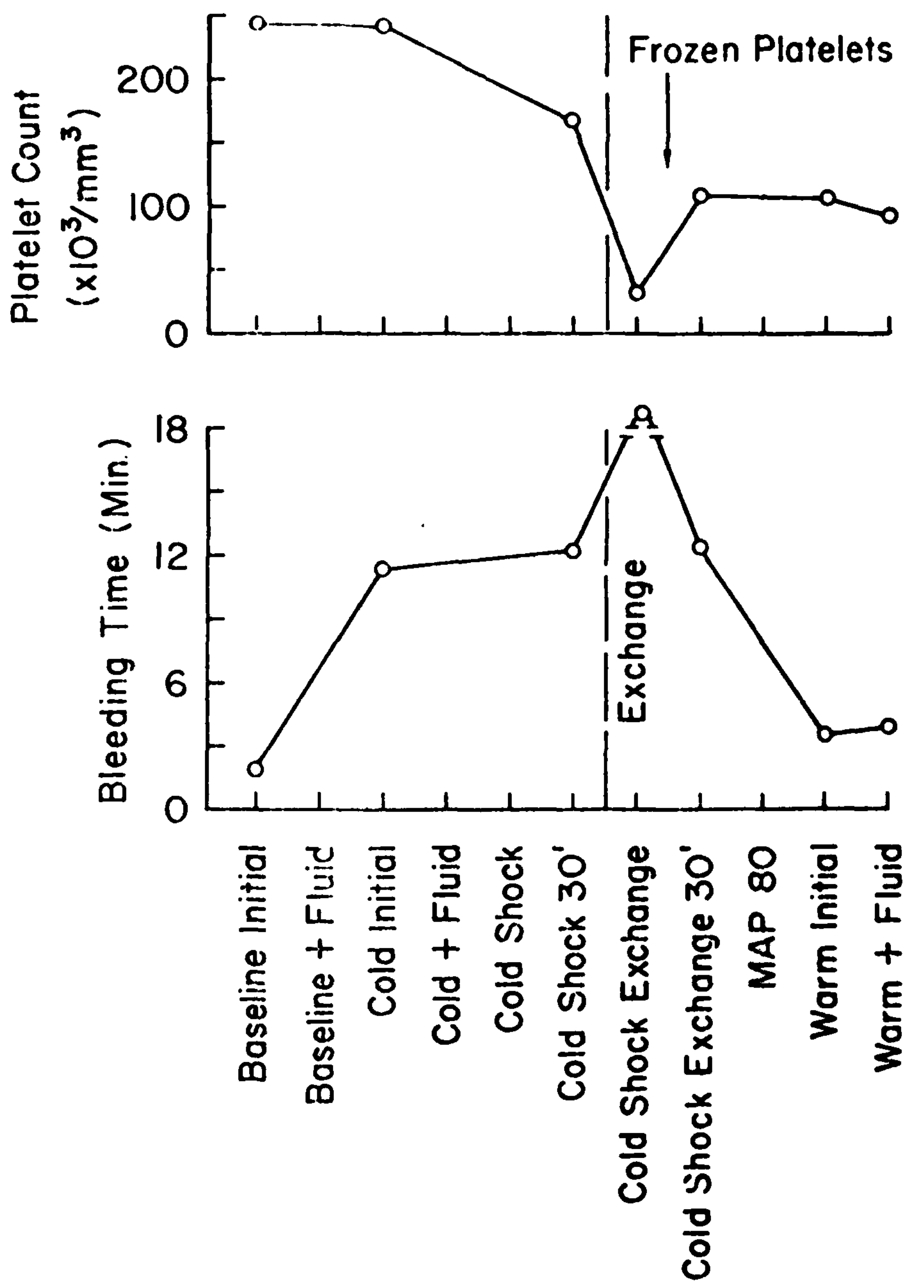

FIGURE 3

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TABLE 1

COMPARISON OF COAGULATION SYSTEMS BETWEEN HUMANS AND BABOONS

CLOTTING ASSAY	HUMAN	BABOON
Prothrombin (sec.)	13.0 ± 1.5	13.4 ± 1.6
Partial Thromboplastin Time (sec.)	31.4 ± 3.4	33.4 ± 3.8
Thrombin Time (sec.)	15.8 ± 0.9	15.9 ± 3.0
Fibrinogen (mg/dl)	179.2 ± 85.6	183.6 ± 93.7
Factor VIII (AHF) (% activity)	74.4 ± 30.0	80.8 ± 24.8
n	20	9

TABLE 2

COMPARISON OF HUMAN AND BABOON PLATELETS

	HUMAN	BABOON
Mean Platelet Volume (u^3)	6.57 ± 0.61 (n = 15)	6.08 ± 0.46 (n = 5)
Platelet Count (x $10^3/mm^3$)	232 ± 58 (n = 9)	325 ± 95 (n = 5)
Number of Dense Bodies Per Platelet	8.70 ± 1.3 (n = 7)	11.2 ± 2.6 (n = 5)
Platelet LDH Activity (IU/10^{10} platelets)	9.47 ± 1.45 (n = 5)	9.48 ± 3.10 (n = 5)

TABLE 3

TEMPERATURE, BLEEDING TIMES AND PLATELET COUNTS

	CORE TEMPERATURE (^{o}C)	WARM ARM TEMPERATURE (^{o}C)	WARM ARM BLEEDING TIME (SECONDS)	COLD ARM TEMPERATURE (^{o}C)	COLD ARM BLEEDING TIME (SECONDS)	PLATELET COUNT (X1000 COUNT/mm^3)
BASELINE INITIAL	36.9 ± 1.0 13	33.6 ± 2.3 9	231 ± 85 9	33.1 ± 2.3 9	237 ± 94 12	248 ± 72 13
+FLUID	36.4 ± 0.8 13					
COLD INITIAL	32.3 ± 0.6 13	33.1 ± 2.9 9	268 ± 119 9	25.3 ± 3.6 9	496 ± 215 12	244 ± 90 11
+FLUID	31.8 ± 0.3 13					
COLD, SHOCK INITIAL	32.1 ± 0.3 10					
30 MIN	32.2 ± 0.2 10	32.2 ± 1.6 6	241 ± 63 6	27.2 ± 1.3 6	376 ± 233 6	172 ± 40 10
COLD SHOCK EXCHANGE INITIAL	31.9 ± 0.9 9	33.0 ± 2.2 6	322 ± 68 6	27.0 ± 1.3 6	372 ± 299 8	44.5 ± 14.8 8
30 MIN	32.1 ± 0.8 9	32.6 ± 1.9 6	543 ± 206 6	27.2 ± 1.1 6	369 ± 266 8	110 ± 43 8
MAP=80	32.5 ± 0.6 9					
WARM INITIAL	36.5 ± 0.8 9	32.6 ± 3.1 6	361 ± 113 6	32.2 ± 3.8 6	407 ± 201 8	89 ± 32 9
+FLUID	36.8 ± 0.5 8					

TABLE 4

COMPARISON OF BABOON AND PATIENT HEMODYNAMIC RESPONSE TO INFUSION OF BLOOD AND FLUID DURING HYPOTHERMIA. THE 18 PATIENTS WERE ANESTHETIZED WITH N_2O, MORPHINE, AND PAVULON, AND RECEIVED TWO UNITS OF BLOOD AND ALBUMIN. THE BABOONS WERE GIVEN PAVULON AND RECEIVED 450 ML OF NORMAL SALINE

	Before Fluid Load		After Fluid Load	
	Patients, n=18	Baboons, n=13	Patients, n=18	Baboons, n=13
C.O. (l/min.)	2.38 ± 0.46	1.96 ± 0.52	3.15 ± 0.71	2.90 ± 0.59
MAP (mm Hg)	84 ± 12	123 ± 24	97 ± 16	129 ± 18
HR (beats/min.)	85 ± 17	126 ± 17.5	78 ± 16	120 ± 15
CVP (mm Hg)	8.4 ± 3.2	6.1 ± 2.3	10.0 ± 2.9	9 ± 2.2
PAWP (mm Hg)	8.7 ± 2.4	7.6 ± 3.3	13.5 ± 4.1	16.7 ± 3.8
TEMP. (°C)	34.5 ± 0.4	32.3 ± 0.6	34.1 ± 0.5	31.8 ± 0.3

TABLE 5

BLOOD GASES

		n	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	pHa	PvO_2 (mm Hg)	$PvCO_2$ (mm Hg)	pHv
BASELINE INITIAL	HIGH 2,3 DPG	(6)	103 ± 8	34 ± 7	7.463 ± 0.047	48 ± 9	38 ± 7	7.441 ± 0.047
	LOW 2,3 DPG	(4)	113 ± 4	27 ± 5	7.550 ± 0.080	45 ± 1	31 ± 4	7.511 ± 0.068
BASELINE +FLUID	HIGH 2,3 DPG	(6)	104 ± 15	33 ± 6	7.450 ± 0.042	51 ± 8	37 ± 6	7.425 ± 0.040
	LOW 2,3 DPG	(4)	113 ± 4	26 ± 5	7.534 ± 0.095	45 ± 1	29 ± 5	7.506 ± 0.088
COLD INITIAL	HIGH 2,3 DPG	(6)	102 ± 9	27 ± 6	7.499 ± 0.048	41 ± 5	30 ± 6	7.479 ± 0.047
	LOW 2,3 DPG	(4)	113 ± 2	20 ± 3	7.597 ± 0.065	35 ± 2	23 ± 4	7.567 ± 0.060
COLD +FLUID	HIGH 2,3 DPG	(6)	105 ± 10	27 ± 5	7.411 ± 0.204	43 ± 3	30 ± 6	7.457 ± 0.044
	LOW 2,3 DPG	(4)	113 ± 3	20 ± 3	7.578 ± 0.066	36 ± 3	23 ± 3	7.560 ± 0.061
COLD SHOCK INITIAL	HIGH 2,3 DPG	(6)	92 ± 19	25 ± 7	7.489 ± 0.066	23 ± 3	31 ± 7	7.447 ± 0.058
	LOW 2,3 DPG	(4)	106 ± 5	18 ± 1	7.594 ± 0.047	19 ± 2	23 ± 2	7.553 ± 0.055
COLD SHOCK +30 MIN	HIGH 2,3 DPG	(6)	91 ± 20	27 ± 8	7.447 ± 0.053	19 ± 3	34 ± 8	7.397 ± 0.056
	LOW 2,3 DPG	(4)	106 ± 5	19 ± 1	7.545 ± 0.047	20 ± 3	26 ± 2	7.489 ± 0.052
COLD SHOCK EXCHANGE	HIGH 2,3 DPG	(6)	90 ± 22	28 ± 8	7.340 ± 0.111	21 ± 3	40 ± 9	7.152 ± 0.162
	LOW 2,3 DPG	(4)	112 ± 4	22 ± 2	7.365 ± 0.038	17 ± 3	29 ± 3	7.300 ± 0.047
COLD SHOCK EXCHANGE +30 MIN	HIGH 2,3 DPG	(6)	96 ± 22	26 ± 9	7.241 ± 0.188	19 ± 3	41 ± 9	7.159 ± 0.177
	LOW 2,3 DPG	(4)	111 ± 4	21 ± 2	7.379 ± 0.060	16 ± 2	31 ± 2	7.315 ± 0.086
MAP 80	HIGH 2,3 DPG	(6)	97 ± 25	30 ± 11	7.173 ± 0.157	40 ± 8	40 ± 9	7.117 ± 0.150
	LOW 2,3 DPG	(4)	111 ± 4	26 ± 3	7.298 ± 0.058	24 ± 7	33 ± 2	7.243 ± 0.053
WARM INITIAL	HIGH 2,3 DPG	(6)	95 ± 17	35 ± 9	7.311 ± 0.126	46 ± 5	43 ± 10	7.247 ± 0.126
	LOW 2,3 DPG	(4)	106 ± 9	28 ± 3	7.423 ± 0.018	37 ± 6	35 ± 4	7.356 ± 0.040
WARM +FLUID	HIGH 2,3 DPG	(6)	98 ± 18	38 ± 12	7.340 ± 0.072	50 ± 5	43 ± 12	7.306 ± 0.070
	LOW 2,3 DPG	(4)	113 ± 2	30 ± 4	7.406 ± 0.027	41 ± 5	34 ± 5	7.378 ± 0.024

TABLE 6

HEMOGLOBIN, P_{50}, BICARBONATE

		n	Hb (gm/dl)	P_{50} IN VIVO (mm Hg)	P_{50} IN VITRO (mm Hg)	HCO_3^- (meq/l)
BASELINE INITIAL	HIGH 2,3 DPG	(6)	14 ± 3	32 ± 5	32 ± 2	25 ± 3
	LOW 2,3 DPG	(4)	15 ± 0.7	29 ± 4	32 ± 1	24 ± 2
BASELINE +FLUID	HIGH 2,3 DPG	(6)	11 ± 2	31 ± 4	32 ± 1	23 ± 3
	LOW 2,3 DPG	(4)	12 ± 0.1	27 ± 2	32 ± 2	24 ± 1
COLD INITIAL	HIGH 2,3 DPG	(6)	13 ± 3	24 ± 3	31 ± 1	23 ± 2
	LOW 2,3 DPG	(4)	14 ± 0.7	21 ± 2	33 ± 2	21 ± 2
COLD +FLUID	HIGH 2,3 DPG	(6)	11 ± 2	23 ± 2	31 ± 2	22 ± 3
	LOW 2,3 DPG	(4)	12 ± 0.6	21 ± 2	32 ± 1	21 ± 1
COLD SHOCK INITIAL	HIGH 2,3 DPG	(6)	10 ± 2	25 ± 2	31 ± 2	20 ± 4
	LOW 2,3 DPG	(4)	10 ± 0.9	22 ± 3	32 ± 2	20 ± 2
COLD SHOCK +30 MIN	HIGH 2,3 DPG	(6)	9 ± 2	26 ± 3	32 ± 2	20 ± 4
	LOW 2,3 DPG	(4)	9 ± 0.8	23 ± 3	33 ± 3	18 ± 1
COLD SHOCK EXCHANGE	HIGH 2,3 DPG	(6)	10 ± 2	34 ± 3	37 ± 3	16 ± 4
	LOW 2,3 DPG	(4)	9 ± 3	22 ± 3	29 ± 2	13 ± 2
COLD SHOCK EXCHANGE +30 MIN	HIGH 2,3 DPG	(6)	10 ± 4	33 ± 3	37 ± 3	10 ± 6
	LOW 2,3 DPG	(4)	8 ± 2	24 ± 3	29 ± 3	14 ± 3
MAP 80	HIGH 2,3 DPG	(6)	11 ± 5	36 ± 3	38 ± 2	12 ± 5
	LOW 2,3 DPG	(4)	8 ± 1	26 ± 2	29 ± 2	13 ± 2
WARM INITIAL	HIGH 2,3 DPG	(6)	12 ± 2	40 ± 3	34 ± 3	18 ± 5
	LOW 2,3 DPG	(4)	11 ± 0.3	32 ± 2	29 ± 3	19 ± 2
WARM +FLUID	HIGH 2,3 DPG	(6)	9 ± 2	41 ± 3	35 ± 2	20 ± 3
	LOW 2,3 DPG	(4)	9 ± 0.4	31 ± 2	29 ± 2	19 ± 2

TABLE 7

BIOCHEMISTRY

		n	CALCIUM TOTAL BLOOD (mg/dl)	CALCIUM IONIZED (mg/dl)	2,3 DPG ARTERIAL (umole/gHb)	LACTATE BLOOD ARTERIAL (umole/ml)
BASELINE INITIAL	HIGH 2,3 DPG	(6)	5.6 ± 1.0	4.2 ± 0.2	16 ± 3	1.6 ± 0.7
	LOW 2,3 DPG	(4)	6.0 ± 0.8	4.3 ± 0.7	17 ± 2	1.5 ± 0.1
BASELINE +FLUID	HIGH 2,3 DPG	(6)	5.1 ± 0.7	3.8 ± 0.2	16 ± 3	1.4 ± 0.7
	LOW 2,3 DPG	(4)	5.8 ± 0.4	3.9 ± 0.3	16 ± 1	1.4 ± 0.1
COLD INITIAL	HIGH 2,3 DPG	(6)	5.5 ± 0.7	4.1 ± 0.4	16 ± 3	2.0 ± 1.4
	LOW 2,3 DPG	(4)	5.9 ± 0.7	4.2 ± 0.3	16 ± 4	2.2 ± 0.8
COLD +FLUID	HIGH 2,3 DPG	(6)	5.2 ± 0.8	3.9 ± 0.2	16 ± 3	2.2 ± 1.7
	LOW 2,3 DPG	(4)	5.7 ± 0.6	4.0 ± 0.1	16 ± 4	2.4 ± 0.9
COLD SHOCK INITIAL	HIGH 2,3 DPG	(6)	5.7 ± 1.0	3.9 ± 0.3	16 ± 3	2.4 ± 1.6
	LOW 2,3 DPG	(4)	5.8 ± 0.5	3.5 ± 0.3	18 ± 4	2.6 ± 0.8
COLD SHOCK +30 MIN	HIGH 2,3 DPG	(6)	5.5 ± 0.7	3.7 ± 0.3	15 ± 4	3.0 ± 1.8
	LOW 2,3 DPG	(4)	5.9 ± 1.3	3.6 ± 0.4	17 ± 4	3.4 ± 1.1
COLD SHOCK EXCHANGE	HIGH 2,3 DPG	(6)	6.2 ± 2.1	2.7 ± 0.6	19 ± 3	3.4 ± 1.7
	LOW 2,3 DPG	(4)	6.5 ± 1.6	2.9 ± 1.1	8 ± 3	4.1 ± 0.9
COLD SHOCK EXCHANGE +30 MIN	HIGH 2,3 DPG	(6)	7.0 ± 2.9	3.6 ± 0.4	20 ± 4	4.1 ± 1.8
	LOW 2,3 DPG	(4)	8.5 ± 1.4	4.5 ± 1.3	8 ± 2	4.9 ± 1.3
MAP 80	HIGH 2,3 DPG	(6)	6.8 ± 3.3	3.2 ± 0.7	20 ± 4	4.4 ± 1.7
	LOW 2,3 DPG	(4)	7.2 ± 1.4	4.0 ± 0.8	6 ± 2	4.8 ± 1.1
WARM INITIAL	HIGH 2,3 DPG	(6)	6.1 ± 2.0	4.3 ± 0.3	18 ± 5	1.8 ± 0.8
	LOW 2,3 DPG	(4)	7.4 ± 1.4	4.2 ± 0.7	8 ± 2	2.6 ± 0.7
WARM +FLUID	HIGH 2,3 DPG	(6)	6.5 ± 0.1	4.1 ± 0.3	20 ± 3	2.1 ± 0.2
	LOW 2,3 DPG	(4)	7.0 ± 1.3	4.1 ± 0.3	7 ± 1	3.1 ± 0.9

TABLE 8

Blood Ionized Calcium Levels Measured at 37 C During Hypovolemic, Hypotensive, Hypothermic Shock Just Prior to Exchange Transfusion, at the Time when a 2:1 Electro-mechanical Dissociation was Observed, and Following the Exchange Transfusion and Replacement Therapy with $CaCl_2$

Study #	Pre-Exchange	Ca^{++} (mg/dl) During Exchange	After Exchange	$CaCl_2$ Given (ml) (10% Soln)
2	2.96	----	2.02	10
3	3.74	----	6.24	10
4	3.96	1.12	1.80	4
5	3.34	0.36	4.52	7
6	3.82	0.64	2.94	7
7	3.96	0.74	2.94	6
8	4.06	1.94	2.58	5.5
10	3.24	1.52	3.28	6
11	3.70	0.62	2.54	5.5
Mean	3.64	1.00	3.20	6.8
SD	.38	.56	1.38	2.0
n	9	7	9	9

TABLE 9

OXYGEN TRANSPORT

		n	CaO2 (ml/dl)	Ca-vO2 BODY (ml/dl)	Ca-vO2 LEG (ml/dl)	VO2 BODY (ml/min)	VO2 LEG (ml/min)
BASELINE INITIAL	HIGH 2,3 DPG	(6)	18 ± 3	4.0 ± 0.9	6 ± 2	3.6 ± 0.3	0.08 ± 0.07
	LOW 2,3 DPG	(4)	20 ± 1	4.2 ± 0.9	6 ± 2	3.3 ± 0.4	0.06 ± 0.02
BASELINE +FLUID	HIGH 2,3 DPG	(6)	15 ± 3	2.8 ± 0.4	4 ± 2	3.8 ± 1.0	0.09 ± 0.06
	LOW 2,3 DPG	(4)	17 ± 1	3.1 ± 0.3	5 ± 2	3.3 ± 0.5	0.06 ± 0.03
COLD INITIAL	HIGH 2,3 DPG	(6)	18 ± 3	2.9 ± 0.7	5 ± 3	2.5 ± 0.2	0.04 ± 0.03
	LOW 2,3 DPG	(4)	19 ± 1	3.4 ± 0.8	7 ± 3	2.5 ± 0.2	0.06 ± 0.02
COLD +FLUID	HIGH 2,3 DPG	(6)	15 ± 3	2.0 ± 0.2	4 ± 2	2.6 ± 0.3	0.07 ± 0.05
	LOW 2,3 DPG	(4)	16 ± 1	2.7 ± 0.5	4 ± 2	2.9 ± 0.6	0.05 ± 0.03
COLD SHOCK INITIAL	HIGH 2,3 DPG	(6)	13 ± 2	7.3 ± 2.0	10 ± 2	2.5 ± 0.3	0.06 ± 0.05
	LOW 2,3 DPG	(4)	14 ± 1	8.3 ± 1.6	11 ± 2	2.5 ± 0.8	0.07 ± 0.06
COLD SHOCK +30 MIN	HIGH 2,3 DPG	(6)	12 ± 3	7.3 ± 1.7	10 ± 2	2.4 ± 0.5	0.07 ± 0.07
	LOW 2 3 DPG	(4)	12 ± 1	7.0 ± 1.1	10 ± 1	2.1 ± 0.4	0.05 ± 0.03
COLD SHOCK EXCHANGE	HIGH 2,3 DPG	(6)	13 ± 3	10.1 ± 2.1	11 ± 2	2.3 ± 0.4	0.06 ± 0.01
	LOW 2,3 DPG	(4)	13 ± 4	8.6 ± 3.4	10 ± 4	2.8 ± 0.9	0.05 ± 0.04
COLD SHOCK EXCHANGE	HIGH 2,3 DPG	(6)	13 ± 5	10.6 ± 4.4	12 ± 5	2.1 ± 0.3	0.04 ± 0.01
	LOW 2,3 DPG	(4)	11 ± 3	8.0 ± 1.9	9 ± 4	2.5 ± 0.1	0.05 ± 0.03
MAP 80	HIGH 2,3 DPG	(6)	14 ± 6	5.3 ± 1.3	9 ± 2	3.1 ± 0.5	0.10 ± 0.06
	LOW 2,3 DPG	(4)	11 ± 2	5.9 ± 1.5	7 ± 2	2.9 ± 0.4	0.06 ± 0.05
WARM INITIAL	HIGH 2,3 DP	(6)	16 ± 3	5.7 ± 1.2	7 ± 2	3.2 ± 0.4	0.10 ± 0.05
	LOW 2,3 DPG	(4)	15 ± 0.4	5.8 ± 1.4	6 ± 1	3.5 ± 0.2	0.08 ± 0.03
WARM +FLUID	HIGH 2,3 DPG	(6)	12 ± 3	4.1 ± 1.3	4 ± 2	4.0 ± 0.6	0.10 ± 0.04
	LOW 2,3 DPG	(4)	12 ± 0.5	3.9 ± 0.6	5 ± 2	3.6 ± 0.4	0.08 ± 0.02

TABLE 10

CARDIOPULMONARY

		n	CI (l/min kg)	FLOW LEG (ml/min kg)	SHUNT (%)	DEADSPACE (%)
BASELINE INITIAL	HIGH 2,3 DPG	(6)	.11 ± .02	2.3 ± 1.8	11.4 ± 4.8	32 ± 3
	LOW 2,3 DPG	(4)	.10 ± .03	1.4 ± 0.6	9.1 ± 1.4	32 ± 9
BASELINE +FLUID	HIGH 2,3 DPG	(6)	.15 ± .03	3.8 ± 2.3	11.6 ± 4.7	27 ± 6
	LOW 2,3 DPG	(4)	.13 ± .03	1.8 ± 0.5	9.1 ± 1.9	30 ± 9
COLD INITIAL	HIGH 2,3 DPG	(6)	.11 ± .02	1.8 ± 0.2	12.4 ± 1.9	25 ± 8
	LOW 2,3 DPG	(4)	.09 ± .02	1.1 ± 0.4	9.8 ± 1.9	22 ± 7
COLD +FLUID	HIGH 2,3 DPG	(6)	.15 ± .02	3.0 ± 0.3	14.2 ± 2.5	22 ± 5
	LOW 2,3 DPG	(4)	.13 ± .03	9.2 ± 0.2	9.7 ± 1.8	24 ± 5
COLD SHOCK INITIAL	HIGH 2,3 DPG	(6)	.04 ± .01	1.2 ± 0.2	5.5 ± 2.7	37 ± 12
	LOW 2,3 DPG	(4)	.04 ± .02	0.7 ± 0.7	3.7 ± 1.0	43 ± 10
COLD SHOCK +30 MIN	HIGH 2,3 DPG	(6)	.04 ± .01	0.9 ± 0.9	5.4 ± 2.7	44 ± 7
	LOW 2,3 DPG	(4)	.04 ± .01	0.5 ± 0.5	3.8 ± 1.1	48 ± 12
COLD SHOCK EXCHANGE	HIGH 2,3 DPG	(6)	.03 ± .01	1.0 ± 1.4	7.2 ± 4.3	52 ± 17
	LOW 2,3 DPG	(4)	.04 ± .01	0.5 ± 0.4	2.5 ± 0.5	42 ± 16
COLD SHOCK EXCHANGE +30 MIN	HIGH 2,3 DPG	(6)	.03 ± .01	0.6 ± 0.5	5.5 ± 2.4	51 ± 12
	LOW 2,3 DPG	(4)	.04 ± .01	0.7 ± 0.4	2.6 ± 0.3	48 ± 14
MAP 80	HIGH 2,3 DPG	(6)	.07 ± .02	1.7 ± 1.0	13.2 ± 8.8	44 ± 20
	LOW 2,3 DPG	(4)	.06 ± .01	1.1 ± 0.2	3.4 ± 0.9	38 ± 8
WARM INITIAL	HIGH 2,3 DPG	(6)	.07 ± .02	1.8 ± 1.0	17.3 ± 9.6	31 ± 2
	LOW 2,3 DPG	(4)	.08 ± .02	1.6 ± 0.6	4.9 ± 1.2	34 ± 11
WARM +FLUID	HIGH 2,3 DPG	(6)	.13 ± .04	2.9 ± 0.4	17.5 ± 13.3	32 ± 8
	LOW 2,3 DPG	(4)	.12 ± .02	2.2 ± 0.4	6.0 ± 0.9	30 ± 4

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